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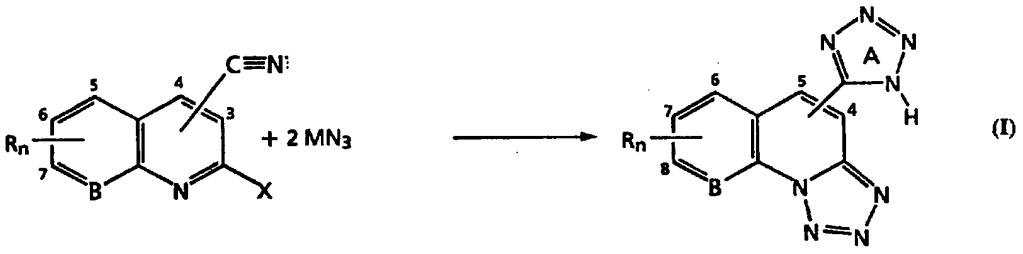
(54) Title: PROCESS FOR PREPARING (1H-TETRAZOL-5-yl)TETRAZOLO [1,5-a] QUINOLINES AND NAPHTHYRIDINES



(57) Abstract

A process according to reaction scheme (I), wherein n is 0, 1 or 2, R is C_{1-4} alkyl, C_{1-4} alkoxy, halogen, methylmercapto, methylsulfonyl, or two R's can be combined as methylenedioxy; B is either nitrogen or CH; and X is a suitable leaving group; M is a lower alkali metal cation; with the proviso that, when R is methylmercapto or methylsulfonyl, then n must be 1.

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PROCESS FOR PREPARING (1H-TETRAZOL-5-yl)TETRAZOLO [1,5-a] QUINOLINES AND NAPHTHYRIDINES

BACKGROUND OF THE INVENTION

The present invention relates to a process for preparing compounds containing two tetrazole rings with one of the tetrazole rings fused into a tricyclic ring system and the second being a substituent on that ring system. Similar compounds described in United States Patent No. 4,496,569 have known utility as antiallergic agents. Particularly, they are useful in the treatment of conditions in which antigen-antibody reactions are responsible for disease, for example, extrinsic asthma, hay fever, urticaris, eczema or atopic dermatitis and upper respiratory conditions such as allergic rhinitis.

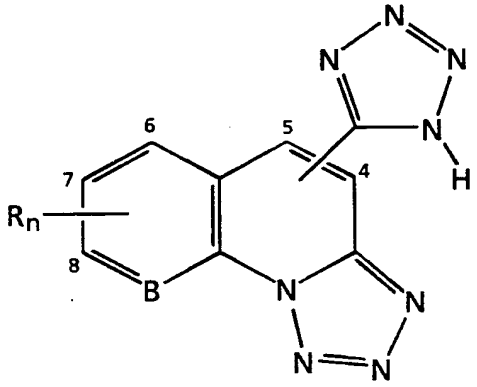
It has heretofore been believed that conversion by azide reaction of a nitrile substituent in a multiple ring system into a tetrazole required the presence of an acid promoter, such as ammonium chloride. In quinolic or naphthyridinoic bicyclic ring systems wherein the primary numbered ring further comprises a 1-α-leaving group and also a nitrile substituent, reaction with azide produces a tricyclic tetrazole-fused compound with a tetrazole substitution replacing the nitrile. Typically, alkali or tetraalkyl azides are used as a common source for azide. However, alkali and tetraalkyl azides were not thought to have been a sufficiently reactive form of azide to convert

a nitrile substituent in a multiple ring system into the corresponding tetrazole.

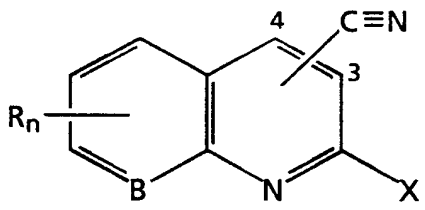
Thus, ammonium chloride was believed to have been necessary in order to convert the sodium azide into the more reactive ammonium azide or hydrazoic acid, which then more easily reacts with the nitrile to form a tetrazole. However, as both ammonium azide and hydrazoic acid are toxic and shock sensitive and hydrazoic acid is extremely volatile, it is desirable to avoid formation and/or use of these compounds in a synthetic scheme.

SUMMARY OF THE INVENTION

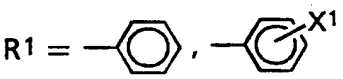
The present invention describes a process for the synthesis of a compound of the formula:



wherein n is 0, 1 or 2; R is C_{1-4} alkyl, C_{1-4} alkoxy, lower halogen, methylmercapto, methylsulfonyl or two R's can be combined as methylenedioxy; B is either nitrogen or CH; with the proviso that, when R is methylmercapto or methylsulfonyl, then n must be 1;
comprising,
reacting in an appropriate solvent,
a nitrile substituted bicyclic compound of the formula:



wherein X is a suitable leaving group such as chlorine, fluorine, bromine, iodine or SO_2R^1, wherein:

R^1 =  , $-C_{1-6}$ straight chain alkyl, $-CF_3$, X^1 is H, $-CH_3$, Br or Cl;

and the nitrile is substituted at either the position marked 3 or 4;

with a suitable amount of an appropriate alkali metal azide or tetraalkyl ammonium azide.

DETAILED DESCRIPTION OF THE INVENTION

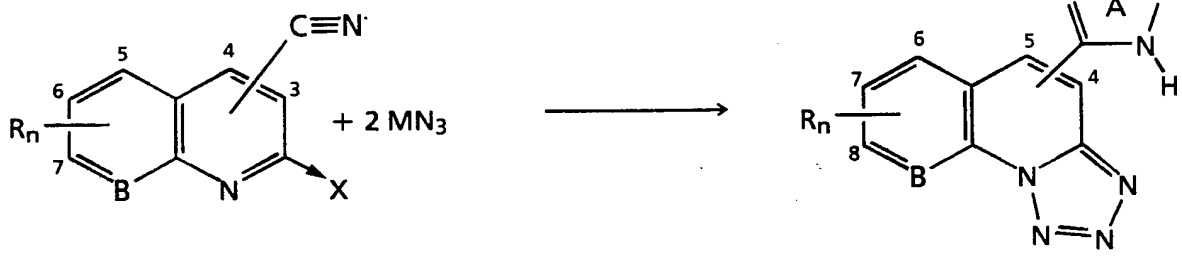
As used herein "C_{1-4} alkyl" means any saturated or branched chain hydrocarbon radical of from 1 to 4 carbon atoms. Included within the scope of this term are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, and the like.

As used herein "C_{1-4} alkoxy" means any saturated straight or branched chain radical containing oxygen and from one to 4 carbon atoms, wherein the radical is centered on the oxygen. Included within the scope of this term are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy and the like.

As used herein "lower halogen" means fluorine, chlorine or bromine.

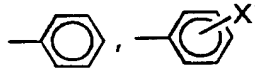
The process of the invention proceeds according to the reaction outlined in Scheme A

Scheme A



Formula I Formula II

wherein n is 0, 1 or 2, R is C_{1-4} alkyl, C_{1-4} alkoxy, lower halogen, methylmercapto, methylsulfonyl, or two R's can be combined as methylenedioxy; B is either nitrogen or CH; and X is a suitable leaving group such as chlorine, fluorine, bromine or SO_2R^1 wherein:

R^1 =  , -C_{1-6} straight chain alkyl, -CF_3, X^1 is H, -CH_3, Br or Cl;

M is a lower alkali metal cation or a tetraalkyl ammonium azide; with the proviso that, when R is methylmercapto or methylsulfonyl, then n must be 1.

The starting material in Scheme A (Formula I), a halocyanide, comprises a nitrile substituent at either position 3 or 4 of the bicyclic ring. The nitrile substituent at the 3 or 4 position of the bicyclic starting compound (Formula I) becomes a tetrazole substituent at the 4 or 5 position, respectively, of the fused tricylic system (Formula II) as indicated. The R substituent may be attached at only the 5, 6 or 7 position of Formula I, and appears at the 6, 7 or 8 position, respectively of Formula II, as indicated. For example, the 5 position of Formula I (bicyclic compound) corresponds to the 6 position of Formula II (fused tricyclic system). In a similar manner, positions 6 and 7 correspond to positions 7 and 8 of the formula II. When n is 0, positions 5, 6 and 7 contain an atom of hydrogen. When n is 1 or 2 and R is not either methylmercapto or methyl sulfonyl, R may be present at any of the positions 5, 6 or 7 or combinations thereof. R may

be methylmercapto or methylsulfonyl when n is 1. When two R groups are combined to form a methylenedioxy, the substitution occurs at adjacent positions. For example, 5 and 6 or 6 and 7.

The nitrile substituted bicyclic starting material is reacted with a suitable amount of an appropriate alkali metal or tetraalkyl ammonium azide in an appropriate solvent under effective time and temperature conditions until formation of the desired end product is complete.

As used herein "appropriate alkali metal azide" means any inorganic azide comprising the azide anion N_3^- and a lower atomic weight alkali metal cation. As example, there may be mentioned lithium azide, sodium azide, potassium azide. The preferred alkali metal azide is sodium azide. As used herein "appropriate tetraalkyl ammonium azide" means an organic azide of the formula "$(R_4N)^+ N_3^-$", wherein R can be a straight or branched lower alkyl of C_1-C_{18}. As examples there may be mentioned tetra-methyl ammonium azide, tetraethyl ammonium azide, tri-methyl-ethyl ammonium azide, dimethyl-diethyl ammonium azide and tetrabutyl ammonium azide.

As used herein, a "suitable amount" an appropriate alkali metal azide can range from about 2.0 to about 5.0 molar equivalents relative to the nitrile substituted bicyclic starting compound. The preferred amount is about 2.1 molar equivalents.

As used herein "appropriate solvent" means a solvating compound suitable for solvating the nitrile and azide reactants in a manner to facilitate formation of a tetrazole. For example, dipolar, aprotic solvents may be employed. As examples, there may be mentioned dimethyl formamide and dimethyl sulfoxide. The preferred dipolar, aprotic solvent is dimethylformamide. Additional solvents

which can be used are dimethylacetamide, N-methylpyrrolidinone, tetramethylene sulfone (sulfolane) and the like.

As used herein, "effective time and temperature" means a reaction time and temperature controlled in a manner so as to facilitate the formation of the reaction product. An effective time is a period sufficient for product formation. It can be dependent upon temperature. An effective temperature is one where the reactants have sufficient energy to react within a reasonable time, but not too energetic so as to cause undesired side reactions, or one where the reaction product degrades. For example, an effective reaction time is generally about 1 to about 48 hours, preferably from about 2 to about 24 hours and most preferably from about 4 to about 8 hours. An effective temperature is generally between about 20°C to about 150°C, preferably from about 90°C to about 125°C and most preferred from about 105°C to about 120°C.

From an appropriately substituted acetanilide can be prepared a starting material which is 2-chloro-substituted, where B is CH, and the nitrile is attached at the three position in Formula I (2-chloro-3-cyanoquinoline). The acetanilide can be heated with phosphoryl chloride and dimethylformamide to give the corresponding 2-chloro-3-quinolinecarboxaldehyde. The process is discussed in detail by Meth-Cohn et al., J. Chem. Soc. Perkin Trans. 1, 1981, 1520, which is herein incorporated by reference. The chloroquinoline carboxaldehyde is then reacted with hydroxylamine hydrochloride, formic acid and sodium formate while heating to give the corresponding 3-cyano-2(1H)-quinolinone. This is then heated with an excess of phosphoryl chloride to give the desired 2-chloro-3-cyanoquinoline.

Alternatively, it is possible to obtain the desired 2-chloro-3-cyanoquinoline directly from an appropriate

acetanilide. The acetanilide is heated with dimethylformamide and phosphorus oxychloride and, after the initial reaction is complete, hydroxylamine (hydrochloride) is added to the reaction mixture and the product indicated earlier is isolated. Thus, cyclization to a quinoline takes place and a cyano substituted product is obtained.

While all of the basic reactants are the same, the latter procedure for preparing the cyano compound differs from the former one in that the reaction is not carried out step wise with isolation of some type of product after each step of the procedure. With this difference in procedure, the actual series of reactant products involved in the two procedures is not identical. Thus, with acetanilide as the starting material, the reaction with dimethylformamide and phosphoryl chloride actually gives, in solution, the cyclized quinoline with a 3-iminium [$-CH=N^{+}=$] substituent. This iminium (salt) can actually be used as such in solution without resorting to an aqueous workup and isolation wherein the iminium is changed to the corresponding (quinoline)-3-carboxaldehyde. In the step wise procedure, the carboxaldehyde is reacted with hydroxylamine to give the oxime which is then dehydrated to the nitrile but, in the course of this reaction in the quinoline procedure under consideration here, the 2-chloro substituent is hydrolyzed to a ketone and an additional separate step is needed to get back to 2-chloro-substitution. In contrast, in the one-step procedure, the iminium salt can be considered as an aldehyde equivalent and it reacts directly with hydroxylamine to give the oxime. But, since an excess of dehydrating agent is present (phosphoryl chloride), the oxime is immediately dehydrated to the nitrile without affecting the 2-chloro atom. Although the procedure is described above for an aldehyde equivalent (iminium salt), it is possible to carry out the same process on aldehydes too. That is, reaction

of an aldehyde with phosphorus oxychloride and hydroxylamine also gives a nitrile directly.

The method above can be generalized to provide a process for the general conversion of an aldehyde or an aldehyde equivalent (such as an iminium salt) to the corresponding nitrile by reaction with hydroxylamine and phosphoryl chloride. The process as described herein can be further generalized to include the immediately preceding step of the formation of an aldehyde or aldehyde equivalent as obtained in the synthesis of the iminium intermediates used in the present application or aldehydes as obtained from an aromatic compound by a Vilsmeier-type reaction.

Example 1

2-Chloro-3-cyanoquinoline (1.89 g, 0.01 mole) and sodium azide (1.37 g, 0.021 mole) were mixed together at room temperature (15°C to 30°C) in 20-25 ml dimethylformamide in a 100 ml round bottom flask equipped with a stirrer, a condenser, and a thermometer. The headspace of the flask was flushed with nitrogen to a bleach scrubber throughout the reaction. The mixture was gradually heated to a preset temperature between 90°C and 125°C until all the mono-tetrazole intermediate disappeared (confirmed by HPLC). This takes typically 2 to 24 hours. Once the reaction is complete, the reaction is cooled to room temperature (15°C to 30°C) and a 1 mL aliquot of 0.01N $NaNO_2$ was added. In a well ventilated hood, the mixture was acidified to pH=2 with dilute HCl to convert any unreacted azide to NO_x and N_2 effluent gases. The resulting solid was filtered and washed with water (25 mL). Yields range typically 90-99% with purity of 98-100% (by weight assay).

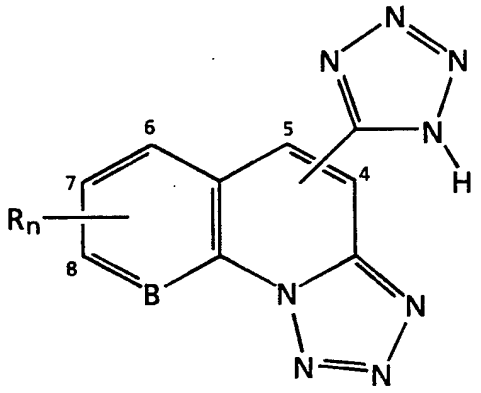
Example 2

2-Chloro-3-cyanoquinoline (30.1 g., 0.159 mol) was added to a suspension of sodium azide (21.75g, 0.335 mol,

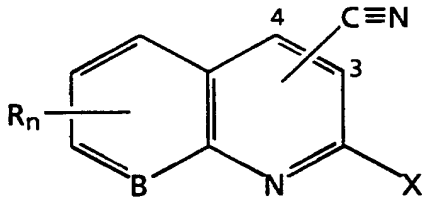
1.05 azide equiv.) in 100 mL of dimethylformamide in a 250 mL 3-neck round bottom flask equipped with a stirrer, a condenser, and a thermometer. The mixture was heated to and held at 115°C for 4.5 hours. The reaction progress was measured by liquid chromatography periodically, where the aliquot diluted with equal volume of water has a pH of 10 to 10.5 throughout the reaction. After the reaction was complete, the mixture was cooled to 90°C and half of the solvent was distilled out under vacuum. The mixture was further cooled to room temperature (15°C to 30°C) and 200 mL of water and 20 mL of 1N-$NaNO_2$ solution was added. The sodium salt of the tetrazole was carefully neutralized with 25 mL of concentrated hydrochloric acid. The resulting suspension was filtered and the wet cake was washed with 300 mL of water. The wet cake was dried to obtain (1H-tetrazol-5-yl)tetrazolo[1,5-a]quinoline.

WHAT IS CLAIMED IS:

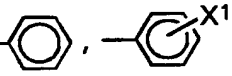
1. A process for the synthesis of a compound of the formula:



wherein n is 0, 1 or 2; R is C_{1-4} alkyl, C_{1-4} alkoxy, lower halogen, methylmercapto, methylsulfonyl or two R's can be combined as methylenedioxy; B is either nitrogen or CH; with the proviso that, when R is methylmercapto or methylsulfonyl, then n must be 1;
comprising,
reacting in an appropriate solvent,
a nitrile substituted bicyclic compound of the formula:

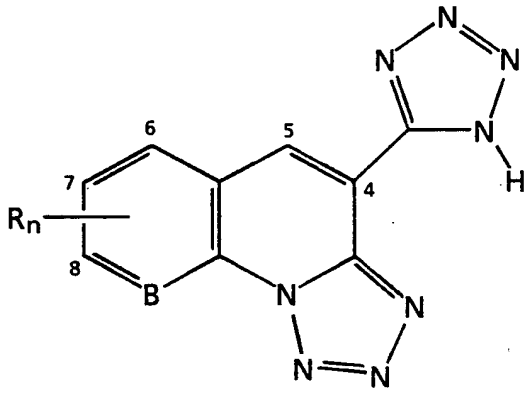


wherein X is a suitable leaving group such as chlorine, fluorine, bromine or SO_2R^1, wherein:

R^1 =  , -C_{1-6} straight chain alkyl, -CF_3, X^1 is H, -CH_3, Br or Cl;

and the nitrile is substituted at either the position marked 3 or 4,
with a suitable amount of an appropriate alkali metal or tetraalkyl ammonium azide.

2. The process of claim 1 wherein the synthesized compound is:



3. The process according to claim 2 wherein the appropriate solvent is a dipolar, aprotic solvent.

4. The process according to claim 3 wherein the dipolar, aprotic solvent is selected from the group consisting essentially of dimethylformamide, dimethyl sulfoxide, dimethylacetamide, N-methylpyrrolidinone and tetramethylene sulfone.

5. The process according to claim 2 wherein the synthesized compound is 4-(1H-tetrazol-5-yl)tetrazolo[1,5-a]quinoline.

6. The process according to claim 2 wherein the synthesized compound is 7,8-dimethyl-4-(1H-tetrazol-5-yl)tetrazolo[1,5-a]quinoline.

7. The process according to claim 2 wherein the alkali metal azide is selected from the group consisting essentially of lithium azide, sodium azide and potassium azide.

8. The process according to claim 7 wherein the alkali metal azide is sodium azide.

9. The process according to claim 2 wherein the tetraalkyl ammonium azide is selected from the group consisting of tetra-methyl ammonium azide, tetraethyl ammonium azide, tri-methyl-ethyl ammonium azide, tri-ethyl-methyl ammonium azide, dimethyl-diethyl ammonium azide and tetrabutyl ammonium azide.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/01967

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 //(C07D471/04,257:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 496 569 (THE DOW CHEMICAL COMPANY) 29 January 1985 cited in the application see column 2, line 10-30 ---	1
A	EP,A,0 177 923 (MERRELL DOW PHARMACEUTICALS) 16 April 1986 see page 3, line 20 - page 3, line 7 ---	1
A	DE,A,21 66 398 (ELI LILLY) 10 January 1974 see page 8, paragraph 2 - page 9 -----	1

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Information on patent family members

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